REMARKS

Reconsideration of this application, as amended, is respectfully requested. Claims 1-46 have been cancelled. New claims 47-72 have been added. With this amendment, claims 47-72 are pending. No new matter is added with these amendments which are made without prejudice or disclaimer. Support for these amendments may be found in the originally filed application. Applicants reserve the right to prosecute any cancelled or otherwise unclaimed subject matter in this or a separate application, as appropriate. Consideration and entry of these remarks and amendments is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

A. Rejection of claims 1-3, 5-7 and 11-17 under 35 U.S.C. § 103(a) over Pouletty in view of Tidey, Chang, and Walter or Baserga

Claims 1-3, 5-7 and 11-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pouletty (U.S. Pat. No. 5,292,641) in view of Tidey et al. (U.S. Pat. No. 6,046,013 ("Tidey"), and further in view of Chang et al. (U.S. Pat. No. 5,270,169 ("Chang")) and Walter et al. (Int. Immunol., Vol. 9, No. 3, pp. 451-459, 1997 ("Walter")) or Baserga et al. (U.S. Pat. No. 6,218,363 ("Baserga")). Claims 1-3, 5-7 and 11-17 have been cancelled; the rejections are therefore moot. However, as new claims 47-67 relate to similar subject matter, Applicants respectfully traverse the substance of the rejections as indicated below in order to expedite prosecution.

As amended, the claims relate to a method for detecting the presence of antibodies "in a body fluid sample" (e.g., blood or serum) reactive to particular MHC or HLA antigens. The claimed methods involve contacting the body fluid sample with recombinant MHC (or HLA) molecules such that antibodies binding to a specific, individual MHC (or HLA) antigen may be identified separately from antibodies reactive to any other specific, individual MHC antigen (e.g, the "one well, one antigen" format described at Applicants' p. 16, line 35 to p. 17, line 8 and p. 23, lines 13-20). To accomplish this, the recombinant MHC (or HLA) molecules are bound to discrete sites upon a solid support so that the antibodies in the body fluid sample reactive with the different specific, individual MHC (or HLA) antigens (e.g., types, alleles) bound to those

sites may be separately detected and identified. Applicants respectfully maintain that the combined cited art does not render the instantly amended claims obvious.

The Office Action alleged that Pouletty disclosed a method of detecting and identifying antibodies to HLA alleles bound (immobilized) to a support (e.g., abstract, col 1- col 3) but that the reference differs from Applicants' claimed subject matter "in failing to teach the HLA antigens are immobilized to discrete sites of the solid support". To fill this gap, the Office Action cited Tidey, alleging that the reference discloses the separate immobilization of 40 different HLA antigens "which are unique from each other. . .to detect the antibodies" (citing Tidey's col. 2 through col. 4). The Office Action alleged that "Pouletty and Tidey et al fail to teach the use of recombinant MHC or HLA molecules" but that Chang "teaches that it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of the HLA epitopes are equivalent to HLA antigens for detection of specific antibodies in a biological sample" (pointing to Chang's col 3, lines 48-62). The Office alleges that one of skill in the art would have a reasonable expectation of success in using such "synthetic HLA antigens" because Walter "discloses that recombinant HLA molecules can be used to detect antibodies in a sample" and Baserga "disclose that MHC or HLA Class I molecules can be produced by recombinant DNA techniques". Thus, the Office Action concludes that the claimed methods would have been obvious to one of skill in the art. Applicants respectfully disagree.

Applicants understand that the references have been cited as a combination and are not attempting to argue against each reference individually outside of the combination. However, it is important to note the distinctions between what the Office Action alleged is taught by each reference and what Applicants believe was actually disclosed in each reference. Accordingly, while some of Applicants' remarks relate to each reference individually, this approach is necessary to show that the references, when combined as set out in the Office Action, cannot render the pending claims obvious.

Tidey is cited as supplementing Pouletty as allegedly disclosing the separate immobilization of 40 different HLA antigens "which are unique from each other. . .to detect the antibodies" (citing Tidey's col 2 – col 4). Applicants respectfully disagree that the Tidey reference makes such a disclosure, and believe the skilled artisan would not understand Tidey's to teach immobilization of individual HLA molecules *per se* to

discrete sites on a solid support as instantly claimed. As described in Applicants' specification, "[t]yping of the numerous HLA molecules present in humans has shown that "individuals possess a particular 'signature' of HLA molecules present on their cells" (p. 1, lines 26-29) i.e., multiple types of HLA molecules. Applicants believe the skilled artisan would understand Tidey to suggest the use of the HLA molecules representing an individual's "signature" (e.g., a "grouping" or "preparation" of multiple HLA molecules), and not individual HLA molecules as instantly claimed. For example, at col. 5 (lines 26-35) Tidey teaches that the "HLA preparations required" represent "forty different HLA types…chosen from may potential donors, each possessing a specific grouping of glycoprotein that is a potential target for an antibody of an immunized person" (emphasis added). Thus, "[i]n a preferred embodiment, a specific HLA glycoprotein from one donor is bound to a microtiter well…each [well] contains a glycoprotein preparation from one of forty donors" (emphasis added). Similarly, Applicants believe one of skill in the art would interpret Tidey's statement at col. 6, lines 57-61 regarding "[f]orty wells containing individual HLA" as referring to the "individual" donor, and not "individual" MHC (or HLA) molecules of the instant claims. In fact, the only actual "HLA preparation" of Tidey is described at col. 8, lines 8-10 as having been "obtained by solubilizing the HLA antigen(s) from human platelets" of 40 different donors. Tidey neither suggests nor makes any effort to separate out the individual HLA molecules from the "grouping" expressed by each donor.

Applicants respectfully maintain that the skilled artisan would understand Tidey to merely relate to a slight variation of the alleged teaching of Pouletty. As stated in the Office Action (pp. 3-4), "Pouletty specifically teaches that a panel of antigens can be used". Tidey similarly teaches the use of a "grouping" or "preparation" of HLA antigens, each "grouping" / "preparation" representing all of the HLA glycoprotein antigens expressed by each of the 40 individual donors. Thus, Tidey merely teaches individual wells containing a "grouping" / "preparation" of HLA molecules representing all of the HLA antigens (e.g., types, alleles) expressed by each of the 40 individuals. As shown in Tidey's Example 4, each of the 34 donors profiled in the table expressed at least four different HLA Class I antigens. In stark contrast, Applicants claimed method relates to isolation and immobilization of recombinant molecules representing distinct MHC (or

HLA) antigens (e.g., types, alleles) at discrete (e.g., distinguishable) locations of a solid support. The claimed methods utilize recombinant MHC (or HLA) molecules such that each of the discrete sites on the soild support only represent one MHC (or HLA) type, and act as the antigen for the antibodies being detected and identified.

As described above, the Office Action cites Chang as teaching that "synthetic HLA antigens...are equivalent to HLA antigens for detection of specific antibodies in a biological sample" (pointing to Chang's col 3, lines 48-62). Accordingly, therefore, it is alleged that one of skill in the art would have a reasonable expectation of success in using such "synthetic HLA antigens" (e.g., in the Pouletty / Tidey method) because Walter "discloses that recombinant HLA molecules can be used to detect antibodies in a sample" or Baserga discloses "that MHC or HLA Class I molecules can be produced by recombinant DNA techniques". Applicants respectfully maintain that Walter is neither predictive nor relevant to the instantly claimed method, and that the characterization of Baserga is technically incorrect (e.g., rendering it irrelevant), as described below.

The Office Action alleged that Walter discloses "detecting the PA2.1 antibodies bound to the A2 complex with goat anti-mouse Ig conjugated to horseradish peroxidase" (p. 452), that "the recombinant molecule can be immobilized and bound by antibody" (p. 456, 1st col.), and that the "recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes" (p. 456, 2nd col.) On page 452 (e.g., Figures 1 and 2), Walter describes the mAb PA2.1 as "specific for HLA-A2 and A28" (e.g. two different HLA alleles) and presents data showing that that particular mouse mAbs may bind recombinant HLA peptide complexes. In Figure 1, mAb PA2.1 is shown to bind HPLC fractions containing HLA-A2 peptide complexes. Binding data relating to another, even less specific, mouse mAb (W6/32) ("specific for HLA-A,B,C") is also described (Fig. 1). In Figure 2, adsorption of HLA-A2 peptide complexes to the surface of HLA-A2 negative cells to which mAb PA2.1 was previously covalently attached is described. Both of these figures merely describe the binding of a purified mAb having specificity for multiple types of HLA antigens to recombinant HLA-A2 complexes. At p. 456, Walter further describes Figure 1 as implying "that the recombinant complexes contain native epitopes, consistent with the presence of correctly folder molecular complexes." It may be correct that Walter's data shows that the mouse

mAb PA2.1, being "specific for HLA-A2 and A28", binds the recombinant HLA complexes produced therein. However, Applicants respectfully maintain that Walter's descriptions are not suggestive or even relevant to the detection of antibodies present "in a body fluid sample" as instantly claimed. The skilled artisan would understand that there is a significant difference between the binding of a purified monoclonal antibody to a recombinant HLA molecule and the detection of a particular antibody present "in a body fluid sample". The skilled artisan would understand that the binding of a mouse mAb to a recombinant HLA molecule would have little, if any, predictive value regarding the instantly claimed method. The "body fluid sample" being tested in Applicants' claimed methods subject matter would be understood by the skilled artisan to typically contain a variety of components and a very low concentration (e.g., especially as compared to a purified mAb preparation) of any particular antibody having specificity for a particular recombinant MHC (or HLA) molecule. In contrast, Walter is using a highly purified preparation of mouse mAb that is not even specific for a single type of HLA antigen (e.g., PA2.1 is "specific for HLA-A2 and A28" (Walter, p. 452)). Accordingly, Applicants respectfully disagree that Walter may be properly relied upon to support Chang's statement regarding "synthetic HLA antigens" and thereby render the instantly claimed subject matter obvious.

Baserga is cited as alternatively providing support (relative to Walter) for Chang's statement regarding "synthetic HLA antigens". It is alleged that Baserga discloses "that MHC or HLA Class I molecules can be produced by recombinant DNA techniques" and that "[t]hese recombinant molecules retain the therapeutic or diagnostic activity of the naturally occurring molecule and provides methods of identifying MHC Class I peptides." The Office Action cites col. 14, lines 10-21 of Baserga, which is reproduced below:

> The MHC or HLA Class I peptides and other compositions of the present invention may be produced by recombinant DNA techniques known in the art. For example, nucleotide sequences encoding MHC or HLA Class I peptides of the invention may be inserted into a suitable DNA vector, such as a plasmid, and the vector used to transform a suitable host. The recombinant MHC or HLA Class I peptide is produced in the host by expression. The transformed host may be a prokaryotic or eukaryotic cell. Preferred nucleotide sequences for this purpose encoding an MHC or HLA Class I peptide are NUCLEOTIDE SEQ ID NOs: 1–13.

Applicants respectfully maintain that Baserga is referring to the production of "MHC or HLA Class I peptides", and not recombinant MHC or HLA molecules *per se*. Baserga's disclosure relates to the isolation and characterization of peptides that are complexed with MHC or HLA molecules in vivo, and not to the production of recombinant MHC or HLA molecules. For instance, at col. 6, lines 11-30, Baserga describes such "MHC Class I peptides" in greater detail:

> Preferred peptides and peptide compositions useful according to the present invention include MHC Class I peptides and, more preferably, HLA Class I peptides, and their variants. Such peptides and variants thereof are generally defined by their capacity to bind to MHC or HLA Class I glycoprotein molecules. Peptides bound by HLA class I molecules are the products of cytoplasmic degradation of cellular proteins that are transported into the endoplasmic reticulum. There they associate with a polymorphic HLA-A, -B, or -C heavy chain and the invariant β_2-microglobulin (β_2-M) to form a stable trimer that moves to the cell surface (S. Kvist and F. Lévy, *Semin. Immunol.* 5:105 (1993). In healthy cells, the peptides are derived from normal cellular proteins, and the immune system is rendered tolerant to these peptides during development. Upon infection of cells, Class I molecules loaded with pathogen-derived peptides are generated and recognized by cytolytic CD8+T cells that then kill the infected cells (A. Townsend and H. Bodmer, *Annu. Rev. Immunol.* 7:601 (1989); R. M. Zinkernagel, *Science* 271:173 (1996).

Accordingly, Applicants do not believe that Baserga is relevant to the instantly claimed methods. As such, Baserga cannot be properly relied upon to support Chang's statement regarding "synthetic HLA antigens" and thereby render the instantly claimed subject matter obvious.

For the reasons stated above, Applicants do not believe the pending claims may be rendered obvious by the combination of Pouletty in view of Tidey, and further in view of Chang and Walter or Baserga. Tidey does not suggest or describe the use of recombinant molecules representing only one individual HLA antigen but only a "grouping" of the same. And neither Walter nor Baserga may be combined with Pouletty, Tidey and Chang to render the instantly claimed methods obvious. Walter relates only to the use of mouse mAbs having at least two specificities, and Baserga does not relate to the use of recombinant MHC or HLA molecules. As explained above, Baserga only relates to the peptide component of an MHC/HLA complex. Accordingly, Applicants respectfully maintain that the cited combination of references cannot render obvious the instantly claimed subject matter.

B. Rejection of claims 20, 24 and 30-42 under 35 U.S.C. § 103(a) over Pouletty in view of Tidey, Chang, Walter, Baserga, and Boguslaski et al. (U.S. Pat. No. 5,420,016 ("Boguslaski"))

Claims 20, 24, and 30-42 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pouletty, Chang, Walter, and Baserga as described in part A above, and further in view of Boguslaski et al. (U.S. Pat. No. 5,420,016 ("Boguslaski")). Claims 20, 24 and 30-42 have been cancelled; the rejections are therefore moot. However, as new claims 68-72 relate to similar subject matter, Applicants respectfully traverse the substance of the rejections as indicated below in order to expedite prosecution.

As described above, Applicants respectfully disagree that the combination of Pouletty in view of Tidey, and further in view of Chang and Walter or Baserga may be relied upon in properly concluding that claims to similar subject matter are obvious. Boguslaski is only cited as teaching assembly of various components into a test kit, which does nothing to satisfy the deficiencies of the primary references. Accordingly, Applicants respectfully maintain that the claims cannot be rendered obvious in view of the cited combination of references. Accordingly, Applicants respectfully request that these rejections be withdrawn.

C. Rejection of claims 25-27 under 35 U.S.C. § 103(a) over Pouletty in view of Tidey, Chang, Walter, Baserga, Boguslaski, and Luxemborg et al. ("Luxemborg")

Claims 25-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pouletty, Chang, Walter, Baserga, and Boguslaski as described in part B above, and further in view of Luxemborg et al. (U.S. Pat. Pub. No. 2004/0137617A1 ("Luxemborg")). Claims 25-27 have been cancelled; the rejections are therefore moot. However, as the new claims relate at least in part to similar subject matter, Applicants respectfully traverse the substance of the rejections as indicated below in order to expedite prosecution.

As described above, Applicants respectfully disagree that the combination of Pouletty in view of Tidey, and further in view of Chang and Walter or Baserga may be relied upon in properly concluding that the claims to similar subject matter are obvious. Luxemborg is only cited as teaching biotinylated recombinant MHC molecules for use in T cell assays, and does nothing to satisfy the deficiencies of the primary references. Applicants respectfully maintain that the claims cannot be rendered obvious by the cited combination of references.

CONCLUSIONS

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned. Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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